Remarks/Arguments

Claims 42-46 and 49-51 are presently pending in this application and are rejected on various grounds. Rejections to the pending claims are respectfully traversed.

Request for consideration of change of address

A Revocation of Power of Attorney and change of address was mailed to the USPTO in this case and a stamped, return postcard was received from the USPTO. Applicants respectfully request that the Examiner note the address change and kindly direct all correspondence pertaining to this case to:

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Claim Rejections - 35 USC § 101 and 35 U.S.C. §112, first paragraph

Claims 42-46 and 49-51 remain rejected under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph for lack of utility.

The Examiner asserts that "the rejection is made for lack of a specific and substantial utility that does not require further experimentation to identify a real world use for the claimed invention." Previously, the Examiner had acknowledged that "the exhibits (previously presented with the response of March 2, 2004) clearly demonstrates that (the) injection of PRO302 protein intra-dermally in guinea pigs will cause some vascular leakage," but the Examiner asserted that "there is no convincing evidence or rational that PRO302 plays any role whatsoever in vascular leakage in its usual role(s) *in vivo*." In the Office action dated January 18, 2005, the Examiner acknowledges that "Example 85 does teach that the PRO302 protein has an effect on vascular leakage when injected into hairless guinea pigs", but asserts that "while the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the actual data or an indication of the relative activity of the PRO302 protein compared to the positive control." Applicants respectfully traverse the rejection.

Utility Standard

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: **"If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."**

Further, according to the Utility Guidelines, "by statute, a patent is required to disclose one practical utility. **If a well-established utility is readily apparent, the disclosure is deemed to be implicit.**" The Guidelines further state that "the record of any issued patent typically reflects consideration of a number of references in the prior art that the applicant or the examiner considered material to the claimed invention. **These references often indicate uses for related inventions, and any patents listed typically disclose utilities or related inventions. Thus, even when the examiner does not identify a well-established utility, the record as a whole will likely disclose readily apparent utilities.....a well-established utility is a specific, substantial and credible utility that must be readily apparent to one skilled in the art."** (Fed. Reg. 66, 1096, 2001, emphasis added).

Arguments

Based on the positive results obtained in the vascular permeability assay, which the Examiner has acknowledged as true based on the evidence presented as exhibits with the previous response, Applicants have asserted a **specific, credible and substantial** role for PRO302 where vascular leakage occurs like in pulmonary leakage, capillary leakage, tumor leakage or burns. Without acquiescing to the propriety of this rejection, merely to expedite prosecution in this case, Applicants file an executed Declaration by Sherman Fong, Ph.D., an expert in the field of immunology, who discusses "the vascular leakage assay" and how this assay identifies molecules that induce leakage, the mechanism of vascular leakage/permeability, how the assay and its modifications have been widely used in the art by several investigators in the identification of various well-established leak inducing molecules like VEGF (VPF) etc. and specific uses. For clarity, Applicants submit that, in the declaration, the assay refers to assay #64 "the skin vascular permeability assay." Applicants submit that both "the vascular leakage assay (Assay #51, Example 85) and "the skin vascular permeability assay (Assay #64, Example 77) are the same. The only difference between the two assays is that the Evans blue dye test of Assay 64 was followed up with a biopsy, and Assay 51, was not followed up with a biopsy after the Evans blue dye test. That is, when one measures vascular "Permeability" versus "Leak" with these assays, one is measuring exactly the same proinflamitory activity. So Dr. Fong's declaration is good for both Assay #51 and Assay #64.

As Dr. Fong explains in his declaration,

> "Proinflammatory molecules can directly or indirectly cause vascular permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. These proinflammatory molecules recruit cells like leukocytes which includes monocytes, macrophages, basophils, and eosinophils. These cells secrete a range of cytokines which further recruit and activate other inflammatory cells to the site of injury or infection. How leukocytes exit the vasculature and move to their appropriate destination of injury or infection is critical and is tightly regulated. Leukocytes move from the blood vessel to injured or inflamed tissues by rolling along the endothelial cells of the blood vessel wall and then extravasate through the

vessel wall and into the tissues (see Exhibit B). This diapedesis and extravasation step involves cell activation and a stable leukocyte-endothelial cell interaction."

In this assay, proinflammatory molecules display blemishes of a previously injected marker dye, a positive exemplary exhibit of which is shown in Exhibit I. Utilities for PRO302 molecule, based on a positive score in the skin vascular permeability assay, such as, to treat inflammatory diseases like autoimmune diseases, psoriasis, etc. are also discussed by Dr. Fong in his declaration. Such utilities would readily be understood, appreciated and accepted by those skilled in the art at the effective filing date as a substantial, credible and specific utility.

Further, Applicants hereby submit patents that were available in the art at or around September 14, 1998 to show that the knowledge as a whole, at that time, for vascular permeability factors was well correlated with diseases where "vascular leakage" is an issue. For example, Dvorak et al., U.S. patent 4,456,550, issued June 26, 1984 disclosed a vascular permeability factor secreted by a hepatocarcinoma tumor cell line that was subjected to the so called Miles assay (see example 4 of Patent 4,456,550), which is very similar to the guinea pig vascular permability assay disclosed in the instant application. Other related assays were also performed to show that the factor identified was distinct from known vascular permeability factors. Based on these results, utility was asserted for this vascular permeability factor in treating tumors. Connolly et al., U.S. patent 5,008,196, issued April 16,1991 further showed that the same vascular permeability factor identified by Dvorak could stimulate endothelial cell growth *in vitro*, while Olander et al., U.S. patent 5,036,003 issued July 30, 1991 disclosed methods of producing an antibody against Dvorak's VPF and Keck et al., U.S. patent 5,240,848 issued August 31, 1993 disclosed the cDNA sequences for the same vascular permeability factor. The art discussed in these patents clearly acknowledged that the Miles assay, an assay very similar to the instant "guinea pig vascular permeability assay," was a well-established assay for determining vascular permeability properties of a molecule and further disclosed that "such factors have therapeutic value as it enables blood nutrients to reach tissues with increased need for nutrients, as in wound healing." The art discussed in these patents further disclosed that "since VPF causes leakage of proteins, including fibrinogen, from blood vessels, thereby initiating the formation of fibrin gel, it may play a role in angiogenesis". Therefore, a positive result in the Miles assay was considered adequate since **the art as a whole disclosed readily**

apparent utilities for vascular permeability factors in diseases which included, but were not limited to, angiogenesis, wound healing, burns, antibodies to treat tumor growth, endothelial cell growth etc. Such asserted utilities in the above issued patents were not considered to be 'general' utilities but rather, were sufficient to meet the statutory requirements for utility. Thus, utilities for VPFs in treating angiogenesis, wound healing (pulmonary or capillary leakage), burns, tumor growth or leakage, etc. are considered to be "well-established utilities" and are not "general" utilities.

The instant application discloses that PRO302 is a novel polypeptide that increases vascular permeability and is considered to be a novel VPF. Based on the 'well-established' utilities for vascular permeability factors in the art as a whole, one skilled in the art would know how to use PRO302 (polypeptides and nucleic acids thereof), or anti-PRO302 antagonists (antibodies) to stop vascular leakage in a variety of diseased conditions associated with leakage, for example, in pulmonary leakage, capillary leakage, tumor leakage, or in burns, at the time of the effective filing date of September 14, 1998 . Applicants further submit that PRO302's utility lies in its use as a target for the development of anti-vascular leakage agents. In rejecting the instant claims, the Examiner asserts that "Applicants have not demonstrated that the protein of the present invention can be used to treat burns, or any wounds." Applicants respectfully remind the Examiner that: "[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996). Based on positive results for PRO302 in the well-established vascular permeability assay, which in turn has been correlated with "well-established utilities," a nexus between PRO302 utility and 'usefulness in disease" has been made by the Applicants which would be considered scientifically sound by one skilled in the art.

In response to the rejection that:

> "while the specification concludes that PRO302 protein can induce vascular permeability in the guinea pig model, it does not give the actual data or an indication of the relative activity of the PRO302 protein compared to the positive control" (emphasis added),

Applicants strongly disagree. In this regard, Applicants respectfully draw the Examiner's attention to **Example 85 (page 216)** which states that:

> "Test samples containing the PRO polypeptide or a physiological buffer without the test polypeptide are injected into skin.....Blemishes of at least 5 mm in diameter are

considered positive for the assay when testing purified proteins, being indicative of the ability to induce vascular leakage or permeability. A response greater than 7 mm diameter is considered positive for conditioned media samples. Human VEGF at 0.1 μg/100 μl is used as **a positive control**, inducing a response of 15-23 mm diameter" (emphasis added).

Therefore Applicants assert that (1) there is a detectable difference between a sample that contained the PRO302 polypeptide injection site and a negative test site that only contained physiological buffer, and (2) the 5 mm diameter blemish for purified PRO302 or 7 mm diameter blemish for PRO302 in conditioned media were compared to a positive VEGF control that gave a 15-23 mm diameter. That is, a relative activity (as compared to physiological buffer and positive control VEGF) has clearly been provided. The Examiner seems to focus on "actual data" (i.e., requiring Applicants to provide exact numbers), but Applicants submit that this is not relevant to the issue at hand, nor is it required for the claimed invention to be useful. What is important for PRO302's utility is the ability in the present application to quantitatively and relatively (say to VEGF) compare the ability of the test molecule, here PRO302, in a reliable assay to produce inflammation (i.e., a blemish). Disclosure of the exact magnitude of size of the blemish for PRO302 is irrelevant as long as Applicants have asserted that the measured difference was significant. Further, Dr. Fong attests that one skilled in the art in this field would consider such a level of inflammation significant and that this assay is routinely used in the art to identify molecules that cause vascular leak and therefore to identify therapies to stop vascular leakage.

Thus, Applicants have asserted at least one "well-established utility" that would be considered specific, credible and substantial by one skilled in the art, for nucleic acids encoding PRO302. Accordingly, Applicants believe that one skilled in the art would know how to make and use the present invention based on the Applicants' disclosure and thus, the present rejection under 35 U.S.C. §101 and §112, first paragraph should be withdrawn.

Claim Rejections - 35 USC §112, first paragraph- Enablement

Claims 42-44, 50-51 remain rejected under 35 U.S.C. §112, first paragraph for lack of enablement.

Based on the discussions above under 35 U.S.C. §101, Applicants have shown that PRO302 polypeptides and their antibodies thereof are useful in treating diseases to stop vascular

leak such as in angiogenesis, wound healing (pulmonary or capillary leakage), burns, tumor growth or leakage, etc. Further, as one skilled in the art would appreciate, PRO302 antagonists, such as anti-PRO302 antibodies, find utilities specifically in stopping vascular leak occurring in a variety of diseases. Further, Applicants submit that any experimentation that may occur towards this use is not undue since a specific, credible and substantial utility has been claimed for PRO302. One skilled in the art would know exactly how to make and use PRO302 from the teachings disclosed in the instant specification. Applicants respectfully submit that in *In re Wands*, the courts concluded that the amount of experimentation needed was not undue in view of the direction and guidance provided by the Appellants and the level of skill in the art. For instance,

> "the court held that ....there was 'considerable direction and guidance' in the specification; there was 'a high level of skill in the art at the time the application was filed;' and all the methods needed to practice the invention were well known." 858 F.2d at 740, 8 USPQ2d at 1406; M.P.E.P. 2164.01(a)

Since the level of skill in the pertinent field at the time of filing was very high, as evidenced by the patents discussed above and the discussions of prior art in these patents, and based on the fact that those skilled in the art generally possessed either an M.D. or a Ph. D or both degrees in addition to vast experience in this field, Applicants submit that, the skilled artisan would find it routine to evaluate PRO-302 polypeptides and would know how to use and stop vascular leaks with anti-PRO302.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the 35 U.S.C. §112, first paragraph, rejections to all pending claims.

Claim Rejections - 35 USC §112, first paragraph- Written description

Claims 42-44, 50-51 remain rejected under 35 U.S.C. §112, first paragraph for lack of showing of possession of the claimed invention.

Applicants maintain, as asserted in the previous response that, Example 14 of the Written Description Guidelines issued by the U.S. Patent Office which clearly states that "protein variants meets the requirements of 35 U.S.C. §112, first paragraph as providing adequate written description for the claimed invention even if the specification contemplates but does not exemplify variants of the protein if (1) the procedures for making such variant proteins is routine

in the art, (2) the specification provides an assay for detecting the functional activity of the protein and (3) the variant proteins possess the specified functional activity and at least 95% sequence identity to the reference sequence". Based on these guidelines, Applicants submit that the instant specification evidences the actual reduction to practice of a full-length native human PRO302 polypeptide of SEQ ID NO: 255, with or without its signal sequence and of the nucleic acid of SEQ ID NO: 254. In addition, the specification provides detailed description about the cloning of variants and describes the gene amplification assay for testing nucleic acids in a PCR based assay. Thus, Applicants submit that the genus of polypeptides of SEQ ID NO: 255 or its variants with 95% identity, further possessing the functional property of "enhancing vascular permeability," would encompass a genus that meets the requirements of 35 U.S. C. §112, first paragraph as providing adequate written description.

Thus, one of skill in the art would know that Applicants had possession of the invention, as described in the instantly amended claims, and therefore request that this rejection be withdrawn.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C39). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

43,626

for Daphne Reddy

Date: July 18, 2005

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